M-I (2) Non-technical abstract. Each year, primary carcinoma of the lung affects more than 170,000 individuals in the United States, making it the leading cause of cancer death for both men and women. Histologically and biologically lung cancer is divided into 2 groups: small cell (20%) and non-small cell (80%). Non-small cell lung cancer (NSCLC) is a major health problem, with only slow advances in therapy over several decades. Based on extensive animal studies, this clinical study will evaluate the concept that transient modification of the genetic composition of tumors to express CD40 ligand (CD40L; a potent activator of dendritic cells) will activate the dendritic cells (DC) within the tumor and the interaction of DC with the different components of the tumor cells will induce trafficking of activated DC to regional immune centers, with induction of tumor-specific immunity. To assess this concept, an adenovirus vector (Ad_{CU}CD40L) will be used to transfer and temporarily express the human CD40L cDNA (gene) in tumors of individuals with NSCLC. The study will be carried out in two phases. First, 12 individuals with inoperable stage IIIb or IV NSCLC will be used to assess safety/toxicity with increasing doses of the Ad_{CU}CD40L vector. Second, once the safety profile is determined, part B will assess the administration of the highest non-toxic dose (as identified in part A) of Ad_{CU}CD40L vector or a placebo (salt water-sugar solution) in a randomized, blinded fashion to NSCLC (stage I) tumors. A total of 20 individuals will be evaluated in part B with surgery for removal of the primary tumor 1, 3, 6 or 10 days after administration of the vector. There is no evidence that delay of surgery for solid tumors for 10 days following diagnosis alters the prognosis. Following administration of the Ad_{CU}CD40L into the lung tumor and its surgical removal, there will be an assessment of cell tumor death (apoptosis), immunohistochemistry and the cytokine (immune related molecules) levels. At the conclusion of the study, the following objectives will be met: (1) to assess the hypothesis that it is safe to administer the Ad_{CU}CD40L vector to lung tumors; (2) to evaluate the hypothesis that intratumoral administration of the Ad_{CU}CD40L vector will result in the activation of DC in the tumor and accumulation of DC and other relevant immune cells in the tumor and regional lymph nodes, with the induction of tumor-specific immunity.